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Review

Translating pharmacogenetics into clinical practice: interleukin (IL)28B and inosine triphosphatase (ITPA) polymophisms in hepatitis C virus (HCV) infection

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Abstract

Hepatitis C virus (HCV) infection is frequently characterized by evolution to chronicity and by a variable clinical course of the disease. The clinical heterogeneities of HCV infection and the imperfect predictability of the response to interferon (IFN) have suggested the need to search for a genetic basis of clinical features. This led to the discovery of genetic polymorphisms playing a major role in the evolution of infection, as well as on treatment response and adverse effects. This review will cover recent reports on the subject, focusing on the potential use of the new genetic markers in the diagnostic algorithm for the stratification of patients for personalized antiviral regimens.

Keywords: hepatitis C virus (HCV); inosine triphosphatase (*ITPA*); interferon (IFN); interleukin 28B (*IL28B*); polymorphism (SNP); ribavirin (RBV).

Introduction

Hepatitis C virus (HCV) is a global health problem, the estimated prevalence of HCV infection is 2.5%, corresponding to about 170,000,000 HCV-positive persons worldwide. Over 70% of acute infections progress to chronicity; an estimated 27% of cirrhosis and 25% of hepatocellular carcinomas (HCCs) occur in HCV-infected subjects (1). The prevalence of HCV infections differs between ethnic groups. While the overall prevalence of HCV infection is similar in the United States, Australia, Turkey, Spain, Italy, and Japan, the age-specific prevalence and genotype distribution are notably different (2). For example, in the United States the prevalence of HCV infection is highest among persons 30–49 years of age (3, 4), while in Mediterranean and Eastern countries, like Japan and China, the age-specific prevalence of HCV infection increase steadily with age, reaching its peak in the sixth decade of life (5, 6).

A marked difference also exists in genotype distribution as well as in the modes of transmission and response to antiviral therapy: genotype 1 is widely present in North America and in Europe, while genotype 2 is most frequent in Japan and China. Genotype 4 is common in Egypt, whereas genotype 5 is found in Southern Africa and is rare elsewhere. Genotype 6 is generally limited to southeast Asia (7–9).

On the whole, available evidence suggests that genotypes do not substantially influence disease severity or progression (8, 9), while they are involved in response to antiviral therapy (8). Standard treatment for chronic HCV infection is based on weekly pegylated interferon (PEG-IFN) doses in association with daily doses of ribavirin (RBV): sustained virological response (SVR) (i.e., maintained clearance of serum HCV RNA 24 weeks after stopping therapy) occurs in about 50% of patients infected with genotype 1 and in 80%–90% of those infected with genotype 2 or 3 (10).

However, there is still a considerable percentage of patients, especially with genotype 1, that do not respond and are at high risk of disease progression to liver cirrhosis and/or HCC. In addition, a percentage of treated patients experience severe side effects that require dose adjustment or treatment discontinuation. Altogether, these considerations have led to investigate other possible co-factors in the attempt to better identify potential sustained responders. Both virus and host characteristics have been previously indicated as relevant determinants of treatment outcome: besides viral genotype, high baseline viral load (11), male gender (11), elevated body mass index (BMI) (12), presence of metabolic syndrome (12, 13) or cirrhosis (14), and menopause (15) are all associated with lower response rate to antiviral therapy. Recently, additional factors linked to the genetic background of patients have been identified and studied in relation to spontaneous or therapy-mediated HCV clearance, and to adverse effects of antiviral treatment. We will focus our review on polymorphisms of interleukin 28B (*IL28B*) (16–22) and inosine triphosphatase (*ITPA*) genes (23), as these are the genetic traits for which relevant and solid information have been established to date.

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Interleukin 28B (*IL28B*) gene polymorphisms

IL28B and spontaneous HCV clearance

The search for a genetic basis for the heterogeneous clinical features of HCV infection was recently approached through the methodology of a genome-wide association study (GWAS). GWAS allows unbiased sampling of variations in the entire genome to assess the relationship between a disease and specific single nucleotide polymorphisms (SNPs) that appear to be more frequent in affected persons compared with controls. This approach consistently found in four independent studies that SNPs located in the *IL28B* gene region are closely related with the events occurring in HCV infection, i.e., spontaneous clearance, rate of progression to chronic infection and sustained response to PEG-IFN/RBV treatment in patients infected with HCV genotype 1 (Table 1).

It is estimated that only about one third of individuals are able to clear HCV while the other progress to chronic infection (31). Factors considered relevant in viral clearance are either those of viral origin (like HCV genotype, inoculum, route, evolution into quasispecies) or those linked to the host (mostly strength of adaptive immune response). However, these factors recently lost some of their relevance (32, 33) while genetic association, especially with polymorphisms in the *IL28B* gene, gained extreme attention (19, 24).

Several studies employing GWAS and genetic mapping have identified a number of SNPs that are in strong linkage disequilibrium (i.e., non-random association), located within or near the *IL28B* gene locus (Table 1). Thomas et al. (19) were the first to study the association of SNP rs12979860 (g.12007005C>T) with spontaneous HCV clearance. They found that individuals with the CC genotype have higher probability of clearing HCV than those with TC or TT genotype. These results were confirmed by Rauch et al. (20) who performed a GWAS in subjects who had cleared the virus either spontaneously or following PEG-IFNα/RBV treatment. Tillman et al. (24) analyzed the relationship between the likelihood of HCV clearance and the *IL28B* polymorphism in a single-source outbreak in a cohort of German women infected with anti-D-contaminated immunoglobulin. In a Spanish cohort, the rs12979860 CC genotype was associated with spontaneous resolution of infection in both males and in females (25).

IL28B and outcome of antiviral therapy

The same IL28B haplotypes associated with spontaneous clearance of HCV were found to be linked to treatment response. The patients from four large studies that evaluated treatment of chronic HCV infection with PEG-IFNα and RBV using a GWAS (Table 1). The first cohort of patients studied was from the ideal study, a head-to-head comparison of PEG-IFNα2a and PEG-IFNα2b for treatment of genotype 1 chronic hepatitis C (16). In this study, more than 500,000 SNPs were considered. Seven SNPs, all located within the IFNλ gene cluster, were found to be related to SVR, but the association could be explained by a single SNP (rs12979860).

Three other groups evaluated the genetic relationship with SVR in a different epidemiological environment (Australia, Japan and Germany). They found that other 2 SNPs, rs8099917 (g.12011383T>G) and rs12980275 (g.12000001A>G) segregated with treatment response (17, 18, 20). On the whole, these data indicate that the IL28B haplotype is a strong determinant of sustained response to PEG-IFNα, although there are significant differences in the overall percentage of SVR explained by the genotypes associated with response. Indeed, this percentage ranges between 55% and 65% of the cohort examined (34): this indicates that other factors still have relevance in determining SVR.

Two additional SNPs, highly associated with rs12979860, were identified by sequencing the *IL28B* gene by Ge et al. (16), that identified a non-synonymous variant within the *IL28B* gene encoding a lysine to arginine substitution at position 70 (g.12003324T>C, K70R; rs8103142) that may potentially affect receptor binding and/or protein stability, together with a C to G substitution (g.12003862C>G, rs28416813) 37 base pairs upstream of the IL28B translation initiation site. Suppiah et al. (18) also identified, in addition to the K70R substitution, that the rs12980275 SNP is strongly associated with non-response. A similar finding was obtained by Rauch et al. (20). Due to the strong linkage disequilibrium among all these SNPs, it is very difficult to disclose the possible causal variant responsible for the association with response to treatment.

The relationship between the *IL28B* genotype and response to antiviral treatment was evaluated also in the setting of liver transplantation. The rs8099917 TT genotype in recipient and donor tissues was found to be significantly associated with the rate of response to treatment in patients with recurrent HCV infection (35). Recently, Akuta et al. (36) identified in a cohort of Japanese patients infected with HCV genotype 1b, a relationship between genetic variation near the *IL28B* gene and amino acid substitution in the core region of HCV as predictors of SVR to a triple therapy of telaprevir/PEG-IFN/RBV.

The possible impact of *IL28B* SNPs in coinfections and other viral infections is the object of ongoing investigation. In patients coinfected with HCV and human immunodeficiency virus (HIV), the rate of response to treatment appears to be influenced by the *IL28B* genotype (37–40). Whether this relationship is limited to genotype 1-infected patients (38), or can be extended to genotype non-1 carriers (39), requires further investigation. Preliminary data indicate that the CC allele may represent an additional predictor of response to PEG-IFNα in chronic HBeAg-negative HBV carriers with genotype D infection (41). In contrast, the rs12979860 SNP does not appear to be associated with the resolution of HBV infection (42), with chronic HBV infection (43) or with HIV infection/disease progression (42, 44).

Epidemiological and clinical correlates of different *IL28B* SNPs

Ge et al. (16) were the first to identify the striking ethnic difference in the frequency of the *IL28B* genotype (CC for SNP rs12979860) associated with SVR. They showed a dis-

Table 1 Studies on the relationship between IL28B genotype(s) and clinical course of acute infection or response to combination antiviral treatment.

Study (references)	Type of study	Characteristics							
		Cohort size	Males	Females	HCV genotype(s)	Geographic area	Ethnicity	Type of response	Relevant SNPs
Ge et al. (16)	GWAS	1137	706	431	1	North America	Caucasian, African American, Hispanic	SVR vs. NR	rs12979860 rs12980275 rs8099917
Tanaka et al. (17)	GWAS	142	n.s.	n.s.	1	Japan	Japanese	VR/SVR vs. NR	rs8099917 rs7248668 rs11881222
Suppiah et al. (18)	GWAS	293	207	86	1	Northern Europe, Australia	Caucasian	SVR vs. NR	rs8099917
Thomas et al. (19)	Candidate gene study	1008	802	206	n.s.	North America	Caucasian, African American	HCV clearance vs. persistence	rs12979860
Rauch et al. (20)	GWAS	465	295	170	1–4	Switzerland	Caucasian	SVR vs. NR	rs8099917 rs8105790
McCarthy et al. (21)	Candidate gene study	231	150	81	1–3	North America	Caucasian, African American	SVR vs. NR	rs12979860
Thompson et al. (22)	Candidate gene study	1671	986	685	1	North America	Caucasian, African American, Hispanic	RVR vs. no RVR SVR vs. NR	rs12979860
Tillmann et al. (24)	Candidate gene study	190	–	190	1	Germany	Caucasian	HCV clearance vs. persistence	rs12979860
Montes-Cano et al. (25)	Candidate gene study	731	418	313	1–4	Spain	Caucasian	SVR vs. NR HCV clearance vs. persistence	rs12979860
Kurosaki et al. (26)	Candidate gene study	496	250	246	1	Japan	Japanese	RVR vs. no RVR SVR vs. NR	rs8099917
Sarrazin et al. (27)	Candidate gene study	267	145	122	1–3	Germany	Caucasian	SVR vs. NR	rs12979860
Mangia et al. (28)	Candidate gene study	268	155	113	2–3	Italy	Caucasian	RVR vs. no RVR SVR vs. NR	rs12979860
Stättermayer et al. (29)	Candidate gene study	682	442	240	1–4	Austria	Caucasian	RVR vs. no RVR	rs8099917 rs12979860
Kawaoka et al. (30)	Candidate gene study	719	403	316	2	Japan	Japanese	SVR vs. NR	rs8099917 rs12979860 rs12980275

SVR, sustained virological response; NR, non-response; RVR, rapid virological response; n.s., not stated.

tinct prevalence between individuals of Caucasian origin in comparison with those of African-American descent. The ethnic disparity in genotype prevalence parallels the known differences in the rates of SVR, although the effect of *IL28B* SNP on treatment response was maintained in all ethnic groups. However, African ancestry remained an independent predictor of non-response (22), which could suggest the presence of other as yet unknown genetic determinants of response to treatment.

The rs12979860 SNP is located just 4378 bases from rs8099917, and is in strong linkage with the latter in Caucasians (16, 20), but not in African-Americans (16) who infrequently show the rs8099917 risk allele (45). Therefore, rs8099917 is not useful for explaining why Africans and persons of African descent are at increased risk of viral persistence and non-response to treatment. Conversely, the rs12979860 TT allele, being more frequent in Blacks than in Caucasians, is a potentially informative marker in populations of African descent. Of further interest is the very high percentage of rs12979860 CC genotype in Asian subjects (16) that may explain the increased SVR rate obtained in those populations, even though clinical trials in Asian patients have not always demonstrated high SVR rates.

The *IL28B* genotype has been related to several clinico-virological features of HCV infection, even if some of these associations need to be confirmed in larger cohorts and in different ethnic groups. The rs12979860 CC genotype appears to be associated with higher pretreatment HCV RNA load (16, 21) and with higher alanine aminotransferase, but lower γ-glutamyltransferase (GGT) activities (25). The wild-type HCV core residues 70 and 91 were detected more frequently in patients with the rs8099917 TT genotype (35, 36, 46), which was also related with lower GGT (26, 46), the absence of steatosis (26) and a higher degree of liver inflammation and fibrosis (46). Another clinical correlation concerns aspects of lipid metabolism in infected subjects: the rs12979860 CC genotype was associated with higher concentrations of total cholesterol, apo-lipoprotein B, and low-density lipoprotein (LDL) (47).

Although the initial data on the clinical relevance of IL28B SNPs were obtained in patients with genotype 1 HCV (16–18), more recently, the degree of association of the IL28B haplotype and clinical features of infection have been investigated in patients infected with different HCV genotypes. An increased frequency of the rs12979860 CC genotype was reported in patients with HCV genotypes 2/3 compared to those with genotype 1 (21, 25, 27, 48), but this relationship was not sufficient to explain the different rates of SVR (21, 25). Concerning treatment outcome in HCV genotypes 2/3, discordant data were reported, two studies in Italian (28) and German (27) patients showing the association of IL28B haplotype with SVR, and two cohorts from Switzerland (20) and Austria (29) failing to confirm the association. A likely interpretation of these results is that since genotypes 2 and 3 are more sensitive to treatment than genotype 1, the impact of the *IL28B* alleles is less evident, and therefore larger series of patients are required to detect statistically significant associations in this setting (49).

A key factor for the understanding of the relationship between *IL28B* genotype and therapeutic response is represented by the kinetics of viral load during treatment. A large study of different ethnic groups showed that the rs12979860 CC genotype was associated with improved early viral kinetics and a greater likelihood of rapid virological response (RVR), which itself represents a strong predictor of treatment outcome regardless of *IL28B* genotype. In addition, a rs12979860 CC genotype was associated with a higher rate of SVR, even in the absence of RVR (22). This observation was confirmed by the detection of a sharper drop in HCV RNA load during the first 24 h of treatment in Austrian carriers of the rs12979860 CC genotype (29). In the same study, when RVR was considered in multivariate analysis of predictors for response, the *IL28B* genotype remained relevant only in patients with HCV genotype 1 (29). In Japanese patients with genotype 2, initial viral load and rs8099917 TT genotype were independent predictors of SVR, and the rs8099917 TT SNP was associated with a steep decline in viral load by the 2nd week of treatment (30). Taken together, these data suggest that despite a general relationship between rs12979860 CC/rs8099917 TT genotypes and RVR, a complex and as yet unclear interplay exists between host and viral factors implicated in the clinical course and therapeutic response of HCV infection.

In this respect, it has been hypothesized that the virological correlates of *IL28B* genotype might reflect the different SNP-related rates of spontaneous resolution (19, 48). The increasing frequency of rs12979860 CC and rs8099917 TT genotypes in uninfected healthy subjects (50%) compared to patients with HCV genotypes 2/3 (45%) and genotype 1 (33%) (21, 28, 48) could be related to the stronger impact of *IL28B* genotype on the clearance of HCV genotype 1 (20). Even the puzzling relationship between the *IL28B* genotypes associated with response and high baseline viremia (16, 21, 27) might result from more frequent resolution of the infection in patients with lower viral loads (48) who can eradicate the infection even in absence of an adequate adaptive immune response (50). The last observation might also offer a clue for the understanding of the increased prevalence of favorable genotypes in healthy seronegative individuals.

Biology and functional role of IFNλ

The product of *IL28B* gene is IFNλ3, an innate cytokine part of the IFNλ family, together with IFNλ1 (encoded by *IL29* gene) and IFNλ2 (encoded by *IL28A* gene) (51, 52). In humans the *IFNλ* genes cluster on chromosome 19 (53). IFNλs are type 3 IFNs, structurally homologous to members of the IL10 family, and are induced by viral infections like type 1 IFNs (such as IFNα and IFNβ). By analogy to type 1 IFNs, the signal transduction of IFNλs is driven by the Jak/STAT pathway and induces the expression of IFN-stimulated genes (ISGs). However, IFNλs exert their action through a distinct receptor, a heterodimer consisting of the interleukin 28 receptor α chain (IL28Rα) and the interleukin 10 receptor β chain (IL10Rβ) (54). In contrast to IFNα and IL10 receptors which are found on various cell types, the IFNλ receptor α chain (IFNλR1 or IL28Rα) is expressed

primarily by epithelial cells, liver tissue and peripheral blood mononuclear cells (51, 52). IFNλ displays additive antiviral and anti-proliferative effects with IFNα, and contributes to the virus-induced increase in the expression of IFN-stimulated genes (ISGs) that activate the innate antiviral immune responses. IFNλ1 (IL29) has recently been used for the treatment of HCV infection with promising results (55).

The biological basis for the relationship between *IL28B* polymorphism and sensitivity of HCV to antiviral treatment is not clear at present. Although the two main *IL28B* SNPs in linkage disequilibrium (rs8099917 and rs12979860) were the same in most of the studies, it is not clear how they exert their influence. It has been postulated that both rs8099917 and rs12979860, being located upstream of the *IL28B* gene, may influence the expression of IL28B. However, results are controversial: no effect on *IL28B* transcription was observed for rs12979860 (16, 56, 57), whereas lower IL28B mRNA levels were detected in association with the rs8099917 GG allele (17, 18, 35). It is worth noting that both rs8099917 GG and rs12979860 TT genotypes are related to increased basal expression of ISGs in the liver of patients with chronic HCV infection (56–58), and that high hepatic ISG levels before treatment are associated with a lack of response to IFN (59–61). This is supported by a recent report that identified ISG expression as the best predictor of treatment response among multiple factors, including *IL28B* genotype (62).

To synthesize the information available at this stage, a model for the influence exerted by *IL28B* genotypes on the clinical course of acute and chronic HCV infection can be hypothesized (63–65), as depicted in Figure 1. In acute infection, HCV triggers the synthesis of IFNα, which in turn enhances IL28B production that has already been induced by the virus itself. The rs12979860 CC and rs8099917 TT genotypes can be associated with stronger IL28B induction (17, 18, 35) or with enhanced cytokine function, leading to increased ISG expression and a higher frequency of spontaneous recovery. The opposite would happen in subjects with rs12979860 TT and rs8099917 GG genotypes. On this line, it has been shown that IL28Rα knockout mice (which

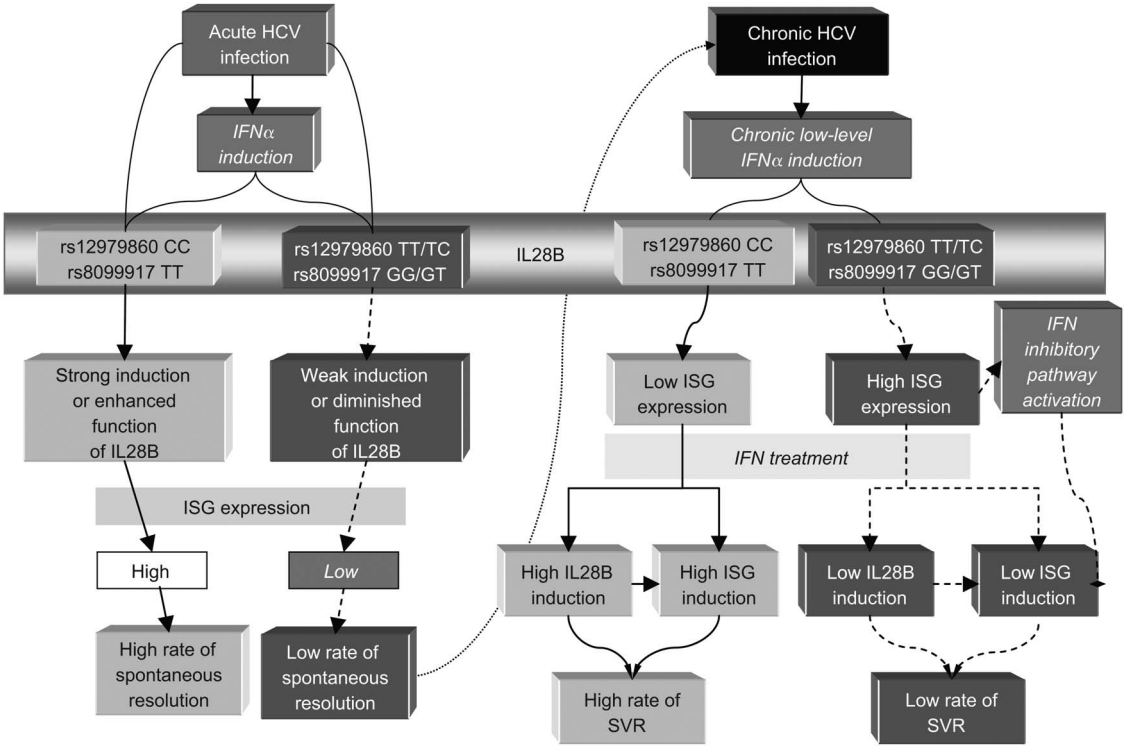

Figure 1 Potential role(s) played by IL28B genotype in acute and chronic HCV infection.
Acute HCV infection (left panel) leads to activation of endogenous IFNα and IL28B production, that is also induced by the viral infection itself and enhanced by IFNα. *IL28B* rs12979860 CC and rs8099917 TT genotypes (continuous line) lead to stronger IL28B induction or enhanced cytokine function, thus increasing the production of IFN-stimulated genes (ISGs) and increasing the rate of spontaneous resolution. In contrast, the *IL28* rs12979860 TT and rs8099917 GG genotypes (dashed line) are characterized by weak IL28B induction, thus increasing the rate of progression to chronicity.
In chronic HCV infection (right panel), low-level endogenous IFNα induces the expression of ISGs. Lower ISG induction is observed in IL28B genotypes associated with response (continuous line). Treatment with IFNα increases ISG and IL28B induction. IL28B may further enhance ISG induction, thus increasing the rate of sustained virological response (SVR). The *IL28B* genotypes associated with non-response (dashed line) are characterized by strong ISG induction in basal conditions and with low ISG and IL28B induction during IFN treatment. ISG and IFN response are further decreased by the activation of IFN inhibitory pathways linked to the basal pretreatment ISG expression. This results in lower rates of response to IFN.

are functionally similar to individuals with the latter genotypes) have severely impaired antiviral response (66).

In chronic HCV infection, sustained HCV replication induces continuous low-level expression of endogenous IFNα and downstream activation of ISGs. rs12979860 CC and rs8099917 TT *IL28B* genotypes, being associated with low basal ISG levels (56–58), allow for stronger activation of IL28B and ISG in individuals being treated with IFNα. In contrast, the high basal ISG expression observed in subjects with rs12979860 TT and rs8099917 GG genotypes impairs further induction by treatment and leads to the activation of IFN inhibitory pathways (60), thus decreasing the possibility of viral clearance.

IL28B genotyping in clinical practice

According to available data, *IL28B* genotyping is a good candidate to become a powerful diagnostic tool for the identification of subjects more likely to respond to antiviral treatments and for the personalization of HCV care. From this perspective, a major issue is represented by the ethnic heterogeneity in *IL28B* genotypes and the consequent variable rates of SVR to combination treatment, ranging from 53% in African-Americans to 82% in Caucasians (16). At present, available data indicate that the most informative target for diagnostic tests is represented by rs12979860 (67), which is the strongest predictor in subjects of African ancestry.

Although the predictive value of *IL28B* genotype in terms of response rate is still insufficient to recommend its use as the only marker for the selection of candidates for therapy, the combination of *IL28B* SNPs and the other known predictors of outcome (HCV genotype, viral load, host characteristics) already allows high accuracy in defining the probability of achieving SVR, as well as the need for a tailored dose and duration of treatment. Further studies should be aimed at the optimization of the pre-treatment diagnostic algorithm for the stratification of patients to personalized antiviral regimens. A better knowledge of viral kinetics in patients with different *IL28B* alleles will be useful to establish whether genotypes associated with clearance could respond to shorter treatment courses, as already occurs for HCV genotypes 2 and 3.

Finally, the relationship between *IL28B* SNPs and viral kinetics might indicate a potential use of genotyping for the selection of candidates and/or for the prediction of response to new treatment regimens, including direct antivirals and/or to IFNλ itself. Although further studies are needed to gain information on this issue, and especially for the definition of the most accurate predictor of outcome between IL28B and RVR, current evidence strongly supports the need of stratification according to *IL28B* genotype at least before inclusion in clinical trials.

Inosine triphosphatase (*ITPA*) gene polymorphisms

Ribavirin (RBV), a synthetic guanosine analog, displays antiviral activity towards RNA and DNA viruses in vitro (68). The effect exerted by RBV on HCV viral load in vivo is minimal (69–71), but RBV and IFN show synergistic antiviral action both in vitro (72) and in vivo (73, 74). RBV antiviral activity seems to result from a direct inhibition of virus replication (75) and cellular GTP synthesis (68), as well as from an effect on the host immune response, through the modulation of the balance between Th1 and Th2 subsets (76).

Anemia is a very common adverse effect of HCV combination treatment, and is the result of RBV-induced hemolysis and of IFN-related bone marrow toxicity. RBV-induced hemolytic anemia (HA) is usually reversible and dose related (73, 74), but may require significant dose reductions possibly affecting efficacy, and is a cause of withdrawal from therapy in 10%–14% of patients (77–81). The molecular mechanism of RBV-induced HA has not been completely disclosed. Oxidative damage and erythrocyte lysis have been related to the intracellular accumulation of pharmacologically active phosphorylated RBV forms, such as ribavirin triphosphate (RBV-TP) and to RBV-induced depletion of erythrocyte ATP content (82).

Several factors are related to the risk of RBV-induced HA: age (83, 84), female gender (83), dose (83) and plasma concentration (85) of RBV, baseline hemoglobin (84) and platelets (86), and haptoglobin phenotype (86). However, even after considering all the above predictive factors, the relevance of RBV-induced HA varies greatly among individuals, suggesting that the genetic background may exert a profound influence on the clinical expression of this adverse effect.

In a recent GWAS, a strong association was shown between hemoglobin reduction after 4 weeks of treatment and SNP rs6051702 (g.3191924A>C) (23). The association was explained by two known functional variants in the *ITPA* gene, located on chromosome 20 and encoding for inosine triphosphatase (ITPase). The two variants, a missense polymorphism in exon 2 (g.3141842C>A, P32T; rs1127354) and a splice-altering SNP located in the second intron (g.8838A>C, rs7270101), results in reduced enzyme activity: homozygosity for the P32T mutation leads to undetectable ITPase activity and accumulation of ITP in erythrocytes (87–90). Both SNPs have already been described as functional variants responsible for ITPase deficiency, a benign inherited red cell enzymopathy (87, 91–93). This condition is characterized by the accumulation of ITP, the substrate for ITPase, in erythrocytes, and increased toxicity of purine analogue drugs (94, 95). Conversely, reduced ITPase activity may be protective from RBV-induced hemolysis through the competition of ITP with RBV-TP (88, 96) and through ITPs substitution of GTP in the generation of AMP, with a protective role against ATP depletion (97).

The results from Fellay et al. (23) have been replicated by Thompson et al. (98), who also reported a strong association between ITPase deficiency and lower frequency of RBV-induced hemolysis over the complete 48-week therapeutic course for genotype 1 HCV. However, even if RBV dose reduction was seldom needed, the treatment outcome was not affected by *ITPA* variants. Recent results by the same group analyzed patients with HCV genotype 2/3, showing that

ITPA variants are protective against treatment-related anemia, but are not related to the rate of SVR (99). In Japanese, the splicing variant-related SNP rs7270101 was not polymorphic (100), but rs1127354 was associated strongly with the incidence and severity of RBV-induced anemia, and marginally with treatment outcome (100, 101).

ITPA genotyping in clinical practice

The *ITPA* genotypes appear to be strongly associated with differential risk of RBV-induced HA and, consequently, of RBV dose reduction. Thus, information on *ITPA* genotype, or alternatively functional ITPAse assays, could play a role in clinical decisions concerning the indication for treatment in patients with co-morbidities, the frequency of hemoglobin monitoring, and the need for dose adjustment. Further studies are needed to assess the clinical use and the cost-effectiveness of this approach, and to examine the potential role of ITPAse activity on the increased risk of anemia induced by new antivirals for HCV treatment that are used in combination with PEG-IFN and RBV (telaprevir, boceprevir) (102). Finally, although ITPase deficiency is associated with increased toxicity of some drugs (purine analogues), the therapeutic modulation of ITPAse activity could represent a promising strategy to prevent RBV-induced HA, improving the compliance to RBV, and eventually the rate of response to combined treatment for HCV infection.

Final statement

In conclusion, the genetic associations previously described are becoming extremely relevant in the decision-making process for patients with chronic hepatitis C. The presence of rs12979860 CC genotype (detected in about 50% of Caucasian people) may have a substantial impact in deciding the indication for treatment. While this is already being done for genotype 1 patients, additional prospective studies are needed to determine the predictive value of rs12979860 genotype among other treatment-eligible patients (different ethnic groups and HCV genotypes other than HCV-1). In contrast, patients with TT or TC rs12979860 genotype may be enrolled in prospective studies evaluating the association of PEG IFN/RBV with protease and polymerase inhibitors to increase the chance of response.

Regarding ITPA polymorphism, its determination can be of great help not only during PEG IFN/RBV therapy, especially for patients at increased risk of anemia, but also in the innovative triple therapies (PEG IFN/RBV/protease or polymerase inhibitors) that are associated with a higher incidence of anemia.

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